REMARKS

Typographical amendments are made to the claims, for example, claims 1, 2, 4-6, 8-16, 29, 31, and 36-45. These amendments are made to make the claims more consistent and definite, and are not intended to limit the claims in any way.

Claim 1 is amended to delete the term "to a computer processor" and add the phrases "the steps of" and "wherein the method steps are performed by a programmable processor executing a program of instructions" as supported in the application, for example at paragraph [0087], page 41 of the specification which states "method steps of the invention can be performed by a programmable processor executing a program of instructions."

New claims 46 and 47 include subject matter corresponding to claims 1 and 31, respectively. New claims 46 and 47 also include the phrase "the binding energy being calculated according to a scoring function selected from the group consisting of subtracting the free energy of the ligand in water from the energy of the ligand in the protein and subtracting the free energy of the protein and the free energy of the ligand from the free energy of the ligand in the protein," which is supported, for example, by claims 13 and 14.

No new matter is added by the preceding amendments.

Applicants' invention

Applicants' invention includes the following steps (Claim1) or instructions for performing these steps (Claim 31):

providing structural information describing the structure of a protein and each ligand in a set of one or more ligands;

using the structural information for the protein to identify a binding region of the protein;

identifying a plurality of preferred binding conformations for each ligand in the set of ligands in the binding region, the preferred binding conformations being determined by generating a set of configurations for each ligand by applying a

coarse-grained docking algorithm and ranking initial conformations for each ligand in the set of ligands at the binding region using energy scoring;

optimizing the preferred binding conformations using annealing molecular dynamics, the annealing molecular dynamics including solvation effects;

calculating a binding energy for each ligand in the set of ligands in the corresponding optimized preferred binding conformations; and

selecting for each ligand in the set of ligands the lowest calculated binding energy in the optimized preferred binding conformations, and outputting the selected calculated binding energies as the predicted binding energies for the predicted binding conformations of the set of ligands,

Applicants' claimed invention provides many significant advantages because the computational effort of the overall task of predicting binding energies is divided among a hierarchical series of identifying, optimizing, calculating and selecting steps that are suited for the level of computation being performed in each step. This strategy can make efficient use of computational resources to lead to accurate predicted binding energies for the predicted binding conformations of the set of ligands.

For example, by employing a coarse-grained algorithm, Applicants' claimed invention allows efficient identification of preferred binding conformations from among possible binding conformations.

Also, by identifying a **plurality** of preferred binding conformations for **each** ligand rather than a single conformation, Applicants' claimed invention does not misplace the burden of identifying a single best conformation on the coarse-grained algorithm. By definition, a coarse-grained algorithm ignores some lower-energy conformations which would be captured by a corresponding fine-grained algorithm, and thus reliance on a single coarse-grained algorithm to identify a single best conformation could miss important results. Rather, Applicants' claimed invention provides that each predicted binding energy for each ligand is selected from among optimized preferred binding conformations.

Further, Applicants' claimed invention reduces the computational requirements of optimization because only the plurality of preferred binding conformations is optimized, rather than all conformations. Relying on a single fine-grained optimization for all conformations would vastly increase the computational burden of predicting binding energies.

Moreover, Applicants' claimed invention increases the chances of obtaining an accurate result because preferred conformations are optimized rather than conformations selected by a procedure that does not identify preferred conformations.

Also, because the computational burden is reduced, the optimization step can afford to use computationally demanding methods such as annealing molecular dynamics that include solvation effects.

Thus, the hierarchical nature of the claimed invention provides an efficient and accurate method for generating predicted binding energies for the predicted binding conformations of the set of ligands.

Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1-6, 8-16 and 29 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Applicants have amended claim 1 to delete the term "to a computer processor" and add the phrases "the steps of" and "wherein the method steps are performed by a programmable processor executing a program of instructions." Applicants respectfully request that the rejection be withdrawn.

Telephone interview summary

The Examiner is thanked for a helpful telephone conversation on March 27, 2006, regarding the rejection under 35 U.S.C. § 112, first paragraph. It was agreed that Applicants' proposed amendment would overcome the rejection of record under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 102(b)

Claims 1-4, 8, 9, 11, 12, 16, 29, 31, 36, 37, 39 and 40 stand rejected under 35 U.S.C. § 102 (b) as allegedly being anticipated by Dewitte et al. J. Am. Chem. Soc., 1996, volume 118, pages 11733-11744 (the Dewitte et al. reference).

However, the Dewitte et al. reference does not disclose each and every element of the invention as claimed. The Dewitte et al. reference employs a "Monte Carlo Molecular Growth Algorithm" (page 11736, column 1, paragraphs 2-6) that results in "preliminary selection of lowest allowed rotamer" [*sic*] (pp 11736, column 1, line 1 of paragraph 5).

By contrast, the claimed invention requires identifying a **plurality of preferred binding conformations** for each ligand in the set of ligands. The "preliminary selection of a single rotamer" in the Dewitte et al. reference is not the plurality of preferred binding conformations required by the present claims. Consequently, the Dewitte et al. reference does not teach optimizing the preferred binding conformations, calculating a binding energy for each ligand in the set of ligands in the corresponding optimized preferred binding conformations, or selecting for each ligand in the set of ligands the lowest calculated binding energy in the optimized preferred binding conformations, as required by the claimed invention.

Further, the claimed invention requires a combination of the identifying step, using a coarse-grained docking algorithm, the optimizing step, using annealing molecular dynamics, and a selecting step, including selecting for each ligand in the set of ligands the lowest calculated binding energy from the optimized preferred binding conformations. By contrast, by teaching the **single** "Monte Carlo Molecular Growth Algorithm" method that immediately settles on the "preliminary selection of lowest allowed rotamer," to identify a ligand complex and optimize to a design energy, the Dewitte et al. reference does not teach or suggest the claimed invention.

Moreover, the method disclosed by the Dewitte et al. reference has numerous limitations:

> SMoG's limitations include those implied in the simple methods in which chemical geometry is handled: interfragment bond lengths and angles are all assumed to be **standard and unvarying**; the protein structure is considered **fixed**; and steric repulsions are either **on or off** depending on a **simple distance test**. (page 11744, colum 2, lines 1-6 of paragraph 4, emphasis added)

Applicants' method, which optimizes the preferred binding conformations using annealing molecular dynamics, the annealing molecular dynamics including solvation effects, is not burdened with the numerous limitations of the method disclosed by the Dewitte et al. reference.

For at least the preceding reasons, the claimed invention is not anticipated by the Dewitte et al. reference, and Applicants respectfully request withdrawal of the corresponding rejection under 35 U.S.C. § 102 (b).

Rejection under 35 U.S.C. § 102(e)

Claims 1-4, 6, 9, 11, 12, 31, 36, 37, 39 and 40 stand rejected under 35 U.S.C. § 102 (e) as allegedly being anticipated by Freire et al. U.S. Pub. App. No. 2001/0000807 (the Freire et al. reference).

However, the Freire et al. reference does not disclose each and every element of the invention as claimed.

For example, the claimed invention requires optimizing the preferred binding conformations using annealing molecular dynamics. The Office Action alleges that with respect to the Freire et al. reference "the algorithm employs structure-based thermodynamic analysis (Fig. 5) (i.e. annealing molecular dynamic), as in instant claim 1 and 31" (page 8, line 9-10). However, this assertion of equivalence between structure-based thermodynamic analysis and annealing molecular dynamics is neither supported by the Freire et al. reference nor scientifically correct. Annealing refers to "simulated annealing," a metaphor for a mathematical technique for combinatorial optimization:

> **Simulated annealing** An *algorithm* for solving hard problems, notably combinatorial optimization, based on the metaphor of how annealing works: *reach a minimum energy state upon cooling a substance, but not too quickly in order to avoid reaching an undesirable final state.* As a heuristic search, it allows a non-improving move to a *neighbor* with a probability that decreases over time. The rate of this decrease is determined by the *cooling schedule*, often just a parameter used in an exponential decay

> (in keeping with the thermodynamic metaphor). With some (mild) assumptions about the cooling schedule, this will converge in probability to a global optimum. (Exhibit A, "Dictionary of Applied Math for Engineers and Scientists," Previato, E., ed. CRC Press LLC, Boca Raton, FL, 2003, p 122; emphasis in original)

Thus, "annealing" is a particular combinatorial optimization method and is not anticipated by the term "structure-based thermodynamic analysis" in the Freire et al. reference.

Moreover, nowhere does the Freire et al. reference disclose the use of simulated annealing as an strategy for any kind of optimization, let alone as annealing molecular dynamics.

Also, the Freire et al. reference does not teach or suggest the plurality of preferred binding conformations for each ligand; nor does it teach or suggest the combination of the identifying step, using a coarse-grained docking algorithm; the optimizing step, using annealing molecular dynamics; the calculating step; and a selecting step, as required by the claimed invention.

For at least these reasons, the claimed invention is not anticipated by the Freire et al. reference, and Applicants respectfully request withdrawal of the corresponding rejection under 35 U.S.C. § 102 (e).

Rejection under 35 U.S.C. § 103 (a)

Claims 1-6, 8-12, 15, 16, 29, 31, 36-40 and 43-45 stand rejected under 35 U.S.C. § 103 (a) as allegedly being obvious over Zuo et al. (1998) (*sic*, apparently Zou, X., et al., J. Am. Chem. Soc. (1999) volume 121, pages 8033-8043), further in view of the Dewitte et al. reference.

The Zuo et al. reference describes the use of the well-known Generalized-Born (GB/SA) model of solvation to estimate ligand binding energies, modifies the GB/SA model to account for electrostatic interactions between the ligand and the solvent, introduces a formula to estimate the binding free energy, and then calculates a free energy score for each conformation of one or more ligands. The resulting scores are used to rank ligands or their conformations, and to explore

appropriate parameters for the model. Thus, the Zuo et al. reference uses a **single** method of conformational search and scoring and retains only **one** conformation.

Accordingly, the single conformation retained by the Zuo et al. reference does not teach or suggest identifying the plurality of preferred binding conformations for each ligand required by the claimed invention.

Further, the single method employed by the Zuo et al. reference does not teach or suggest the combination of the identifying step, using a coarse-grained docking algorithm; the optimizing step, using annealing molecular dynamics; the calculating step; and a selecting step, as required by the claimed invention.

Also, the exhaustive methods of the Zuo et al. reference are computationally demanding, and the Zuo et al. reference precalculates certain quantities and cuts-off calculation of others in order to implement these methods (page 8036, section 5). By contrast, the claimed method employs identifying, optimizing, calculating and selecting steps that are separated by the level of computation being performed in each step, which can efficiently and accurately lead to predicted binding energies for the predicted binding conformations of the set of ligands.

As noted above, the Dewitte et al. reference does not teach or suggest the step of identifying the plurality of preferred binding conformations, nor does it teach or suggest the claimed combination of the identifying step, using a coarse-grained docking algorithm; the optimizing step, using annealing molecular dynamics; the calculating step; and a selecting step, as required by the claimed invention. Therefore, the Dewitte et al reference does not remedy the defects of the Zuo et al reference.

Thus, even when combined, the Zuo et al. reference and the Dewitte et al. reference do not teach or suggest the requirements of the claimed invention, including identifying a plurality of preferred binding conformations for each ligand in the set of ligands in the binding region, the preferred binding conformations being determined by generating a set of configurations for each ligand by applying a coarse-grained docking algorithm and ranking initial conformations for each ligand in the set of ligands at the binding region using energy scoring; and optimizing the

preferred binding conformations using annealing molecular dynamics, the annealing molecular dynamics including solvation effects.

For at least these reasons, the claimed invention is not obvious over the Zuo et al. reference in view of the Dewitte et al. reference, and Applicants respectfully request withdrawal of the corresponding rejection under 35 U.S.C. § 103 (a).

New claims

Applicants note that claims 13 and 14 would appear to be allowable but for the 35 U.S.C. § 112 rejection, which is now overcome. Applicants have added new claim 46 which includes the subject matter of claims 13 and 14 via the phrase "the binding energy being calculated according to a scoring function selected from the group consisting of subtracting the free energy of the ligand in water from the energy of the ligand in the protein and subtracting the free energy of the protein and the free energy of the ligand from the free energy of the ligand in the protein." New claim 46 also includes the subject matter of independent claim 1, on which claims 13 and 14 depend. Likewise, new claim 47 includes the subject matter of claims 13 and 14 in combination with the subject matter of claim 31. Thus, it is believed that new claims 46 and 47 are patentable and their allowance is earnestly solicited.

Conclusion

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's objections and rejections are hereby requested. Allowance of the claims is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (650) 839-5078.

Enclosed is a $225.00 check for the two-month extension of time fee. Please apply any other required charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: Apr. 28, 2006

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